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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,840	05/17/2007	Maureen Caligiuri	GPC-298.1P US	2801

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EXAMINER	
PAGONAKIS, ANNA	

ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,840	CALIGIURI ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-107* is/are pending in the application.

4a) Of the above claim(s) *43,44,48-51,53-56,61,62 and 66-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42, 45-47, 52, 57-60 and 63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 10/15/2010 have been received and entered into the present application.

Applicant's arguments filed 10/15/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Applicant alleges that claims 39-47, 52-55, 57-65 and 70-72 should be under examination because the method does not require the administration of a taxane. This is not found persuasive. Applicant is guided to the Election of Species Requirement made on 3/31/2009 which required the election of "the presence or absence of a taxane (**see for example instant claims 43-44, 61-62, 78-79 and 95-96**). Applicant subsequently elected the absence of a taxane on 6/2/2009. Therefore, it is clear in the election of species that the election was drawn to the instant claims.

Status of Claims

Claims 39-107 are pending.

Claims 43-44, 48-51, 53-56, 61-62 and 66-107 remain withdrawn.

Claims 39-42, 45-47, 52, 57-60 and 63-65 are currently under examination and the subject matter of the present Office Action.

Maintained rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-42, 45-47, 52, 57-60 and 63-65 are rejected under 35 U.S.C. 112, first paragraph, as failing

to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include (1) the quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability in the art, and (8) the breadth of the claims."

The nature of the invention

Claims 39-42, 45-47, 52, 57-60 and 63-65 are drawn to a method for an individual with a tumor resistant or refractory to a taxane, comprising administering to the individual a compound of claim 39.

The breadth of the claims

The claims encompass a method of treatment of a patient who is suffering from a tumor resistant or refractory to a taxane comprising administration of a compound of claim 39. The experimental results presented are in an *in vitro* setting.

The unpredictability of the art and the state of the prior art

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonably degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York., p4) teach that it is recognized in the art that there are many differences between cultured cells and counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissues are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4., see Differences in Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is note. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been scientific characteristics different form those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed since forma screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, column one) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Working examples

The specification provides working examples of:

(1) efficacy of satraplatin is maintained in taxane-resistant tumor cells (page 50 of the instant specification);

(2) efficacy of satraplatin is maintained in camptothecin-resistant tumor cells (page 53 of the instant specification);

(3) efficacy of satraplatin is maintained in tumor cells in which resistance is mediated through ATP-binding cassette (ABC) transports (page 55 of the instant specificaiton);

(4) efficacy of satraplatin is maintained in cisplatin resistant tumor cells (page 57 of the instant specification).

Thus, while the specification demonstrates the in vitro activity of the elected compound, the specification appears to be silent on any suggestion between the in vitro testing and in vivo success. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Guidance in the specification

The specification of the instant applicant provides little guidance in terms of treating or preventing cellular proliferation in vivo.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high level of skill in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claims as broadly written.

Response to Applicant's Remarks

Applicant alleges that the Examiner is disregarding the submitted data which demonstrates a platinum-based chemotherapeutic agent is effective at killing tumor cells resistant or refractory to a taxane in a widely-accepted model of cancer. Applicant goes on to summarize the submitted results. This is not found persuasive. Applicant's attention is drawn to the rejection which specifically stated the following:

> The claims encompass a method of treatment of a patient who is suffering from a tumor resistant or refractory to a taxane comprising administration of a compound of claim 39. **The experimental results presented are in an *in vitro* setting.** (page 3 of the Office Action, emphasis added)

Therefore, in contrast to Applicant's allegations, the submitted data has in fact been considered.

Applicant contends that the Gura article was written over seven years after the Gura article and is a personal statement. This is not found persuasive. Applicant seems to be implying that the age of the Gura article somehow invalidates its teachings. It should be noted that Applicant has not set forth any evidence contrary to the teachings of Gura. It is well known in the art that in vitro efficacy does not necessarily correlate to in

vivo efficacy. In fact, according to Agarwal (Nature, Cancer, July 2003, Vol. 3) "despite the increase in the number of drug-resistance mechanisms that have been described in vitro, so far none of these mechanisms has been shown unequivocally to be important in the clinical setting" (page 508, paragraphs of bridging columns 1-2). As such, the teachings of the Gura reference still appear to hold true. Further, Applicant has not addressed why the age of the reference renders its teachings irrelevant. Applicant fails to advanced any specific reasons or evidence, aside from Counsel's own allegation, in support of this position that no motivation exists in the present obviousness rejection. This assertion by Counsel is an unsupported allegation and fails to take the place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP 2145, which states "The arguments of counsel cannot take the place of evidence in the record."

Applicant alleges that the effectiveness of the drug has been established in humans and therefore predictive value of the model for a new drug of unknown effectiveness is of little relevance here. It appears that Applicant's argument one would necessarily expect in vivo efficacy of an agent in drug resistant tumor cell lines given that this same agent is known to be effective in non-drug resistant tumor cell lines. This is not found persuasive. As taught by Agarwal et al., there has been difficulty in translating in vitro data on mechanisms of drug resistance and its modulation in tumors in patients. Specifically, response rates of only 5.6 to 6 percent have been observed in recent trails in platinum-refractory ovarian cancer. These results have been observed with well known agents such as ZD-0473, BBR-3464 and oxaliplatin (page 512, column 1, first paragraph).

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 7am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/

Supervisory Patent Examiner, Art Unit 1628